REMARKS

In the present response, claims 12-20 are amended, claims 24-26 are added, and no claims are cancelled. Therefore, claims 10-26 are pending in the application with claims 10 and 17-23 being independent.

Explanation of Amendment

By this amendment, Applicants amend claims 12-16 to be more consistent with independent claim 10. Applicants also amend claim 16 to recite at least one influenza antigen. Method claims 17-20 are amended to delete "step" language. New dependent claims 24-26 further define the at least one particulate immunogen.

Applicants submit that each of the foregoing amendments is fully supported by the specification. For example, support for reciting at least one influenza antigen is found in the description of "at least one . . . immunogen," which, based on the context of the present application, would be understood to include at least one influenza antigen. See e.g., present application at page 4, lines 15-16; and page 7, line 30.

Applicants submit that these amendments clarify the claims, but do not in any way narrow the scope of the claims, such that no estoppel should be deemed to attach thereto. Accordingly, no new matter has been added by the amendments and no estoppels are intended thereby.

Response to Objection to Specification

The Office requests that the trademark EPISERF be capitalized wherever it appears and be accompanied by the generic terminology. Office Action at page 2. In response, Applicants have amended the specification to recite "EPISERF cell culture

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medium." Applicants submit that this term, or medium, is known in the art and does not constitute new matter.

In view of the above, Applicants respectfully submit that this ground of objection should be withdrawn.

Response to § 112, First Paragraph, Rejection

Claims 10-23 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Office asserts:

> . . . the specification, while being enabling for a vaccine comprising LTB ans [sic, and] influenza hemagglutinin, as well as methods of inducing an immunoglobulin response against influenza HA and methods of preparing LTB and influenza HA, does not reasonably provide enablement for any vaccine comprising any immunogen, methods of preparing any vaccine and methods of inducing a mucosal response against any immunogen.

Office Action at page 3. According to the Office, the "claims encompass a myriad of immunogens which includes vaccines against HIV. The specification does not enable the broad scope of the claimed invention." Id.

In response, Applicants initially note that the present claims are not so broad as to cover "any vaccine comprising any immunogen." Instead, for example, independent claim 10 recites "[a] vaccine composition comprising at least one particulate immunogen and an adjuvanting amount of B subunits of heat-labile enterotoxin characteristic of *E. coli*, wherein said B subunits are free of A subunit and toxic LT holotoxin." Contrary to the assertions of the Office, Applicants respectfully submit that particulate immunogens do not include all immunogens. See present application at, e.g., page 4, lines 4-13, for a discussion of the role of a particulate immunogen in the present invention. Similarly, independent claim 23 recites "[a] vaccine comprising at least one immunogen and an

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adjuvanting amount of B subunits chosen from enterotoxin and cholera toxin, wherein said B subunits are free of A subunit, toxic LT holotoxin, and toxic CT holotoxin."

Additionally, Applicants note that a B subunit of heat-labile enterotoxin (LTB) is a general mucosal immunoadjuvant that stimulates a systemic and mucosal immune response. The Office has failed to show or provide any reasoning demonstrating that this adjuvant activity does not occur with any particulate immunogen. In fact, the adjuvant activity of LTB has been shown in mice not only for particulate influenza virus subunit antigen, but also for a number of different particulate immunogens, including *Streptococcus pneumoniae* pneumolysin and Diptheria toxoid, as well as keyhole limpet hemocyanin. See De HAAN et al., "Non-toxic variants of the *Escherichia coli* heat-labile enterotoxin as mucosal immunogens and adjuvants," *S.T.P. Pharma Sciences*, 8(1):75-80 (1998); and De HAAN et al., "Mutational analysis of the role of ADP-ribosylation activity and G_{M1}-binding activity in the adjuvant properties of *Escherichia coli* heat-labile enterotoxin towards intranasally administered keyhole limpet hemocyanin," *Eur. J. Immunol.*, 28:1243-1250 (1998), respectively, both submitted herewith.[1]

Regarding the Office's objection concerning vaccines against HIV, Applicants note that the Office has failed to show or provide any reasoning that a vaccine formulation including at least one particulate antigen derived from HIV and LTB or CTB would not induce an enhanced immune response against the immunogen (relative to the response induced by the immunogen alone). This enhanced immune response, however, may not always protect against infection for a long time, due to the genetic

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[1] Note that these articles are submitted in response to an issue raised in the Office Action. Thus, these articles are submitted as evidence directed to an issue of

variability of HIV. Thus, an induced and LTB- or CTB-stimulated immune response may not always neutralize the virus, because HIV may have changed its antigenic structure in the meantime. Therefore, the protection that is induced initially may not remain, as a result of a mismatch between the vaccine-induced antibodies and the virus. In other words, there may be an induced protection, but it may be short-lived. This, however, does not imply that LTB and CTB fail to act as immunoadjuvants and that the vaccines of the present invention would not function against HIV.

Applicants remind the Office that the case law defining and explaining the enablement requirement of 35 U.S.C. § 112 does not prohibit some experimentation to practice Applicants' claimed invention. See *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Further, U.S.P.T.O. policy guidelines indicate that enablement is usually established when a genus is claimed, examples are provided, and a general statement applicable to the genus is made:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art--in view of level of skill, state of the art and information in the specification--would expect the claimed genus could be used in the manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

"Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph -- Enablement Chemical/Biotechnical Applications" (hereinafter "Enablement Training Materials"), page 28.

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patentability raised in an Office action. Accordingly, payment of a fee should not be necessary for consideration of these articles. See M.P.E.P. § 609 III. C(3).

In the present case, Applicants use language in the specification which is commensurate in scope with the claims to describe the enablement of the invention, (see e.g., specification at page 1, lines 3-6; page 4, lines 15-17), and the Office Action does not allege that the examples do not function as described in the specification. Therefore, the claims are enabled at least for the reasons stated in the "Enablement Training Materials."

Still further, Applicants are entitled to claims that are directed to their broader disclosure so as to provide the level of protection that is commensurate with their invention. The court stated in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), at page 218 (emphasis in original) (footnote omitted):

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

As in *In re Angstadt*, Applicants have provided sufficient guidance for one having ordinary skill in the art to make and use Applicants' invention without undue experimentation or effort or expense. Using the guidance disclosed in Applicants'

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originally filed specification, immunogens that are within the scope of the invention can be determined. Conversely, without undue experimentation or effort or expense, immunogens that are not within the scope of the invention can also be determined.

In particular, with the guidance provided in the originally filed application with respect to the characteristics of the immunogens, any experimentation required would not be undue and certainly would not "require ingenuity beyond that to be expected of one of ordinary skill in the art." See *In re Angstadt*, 190 USPQ2d at 218, *citing Fields v. Conover*, 170 USPQ 276, 279 (CCPA 1971).

Even further, the claimed invention does not have to exclude less preferred embodiments. Applicants point out that *In re Angstadt* stands for the proposition that it is unnecessary to disclose every "catalyst" which will work or every "catalyst" which will not work. Additionally, the Court indicated in *In re Anderson*, 176 USPQ 331, 334-335 (CCPA 1973), that claims are not too broad merely because they are not somehow limited to operative or suitable medicants, even though there may exist some medicants that may be unsuitable for use in the dressing of the invention. Moreover, even if some of the claimed combinations are inoperative, the claims are not necessarily invalid as long as the number of inoperative combinations does not result in undue experimentation. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984).

In view of the above remarks, and in view of the discussion in the present specification, Applicants respectfully submit that a skilled artisan would be able to practice the present invention without undue experimentation.

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Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Response to § 112, Second Paragraph, Rejection

Claims 10-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Office, the "claims are indefinite in the recitation of 'characteristics of *E. coli*' . . . ." Office Action at page 5. The Office also asserts that "disease which is transmitted by mucosal infection," "characteristic of a micro-organism," "common mucosal immune response," and "sufficient quantity" are indefinite. Id. at 6. The Office further asserts that claims 12 and 23 are indefinite for being in improper Markush format. Id.

In response, Applicants respectfully submit that the present claim language is definite. According to § 2173.02 of the M.P.E.P.:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Thus, definiteness is assessed in view of the application, the teachings of the prior art, and claim interpretation by a skilled artisan.

Regarding "characteristic of *E. coli,*" Applicants respectfully submit that this phrase is clear at least in view of the discussion in the specification and what is known in the art. The specification, at page 1, lines 3-6, discusses B subunits of heat-labile enterotoxin (LTB) of *E. coli.* In view of this discussion and in view of what is known in the art, Applicants submit that this phrase would be understood. For example, in the present context, "characteristic of *E. coli*" would, at least, include B subunits of heat-

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labile enterotoxin from *E. coli* and B subunits of heat-labile enterotoxin made recombinantly from the *E. coli* B subunit sequence, e.g., polynucleotide sequence. The B subunits of heat-labile enterotoxin also function as an adjuvant, since the claims recite an adjuvanting amount.

Regarding "disease which is transmitted by mucosal infection" of dependent claims 13-15, Applicants respectfully submit that the scope of this language is clear to the skilled artisan. If this ground of rejection is maintained, Applicants request clarification of the rejection.

Concerning "characteristic of a micro-organism" of dependent claim 14, Applicants respectfully submit that this language is clear in the context of this claim and what is known in the art. For example, "characteristic of a micro-organism" would include immunogens from micro-organisms which cause a disease that is transmitted by mucosal infection and immunogens made recombinantly from a sequence, e.g., polynucleotide sequence, of such a micro-organism.

Concerning "common mucosal immune response" of independent claim 20, Applicants respectfully submit that this language is clear in the context of this claim and what is known in the art. For example, a "common mucosal immune response" would include a mucosal immune response normally caused by an immunogen. Also, note the discussion on page 2, lines 15-29, of the present application. Still further, note that Example 6 of the present application shows a response at a distant mucosal site, showing that responses may be found at more places than just local.

Regarding "sufficient quantity" of independent claims 17-20, Applicants respectfully submit that this language is clear in the context of the present claims.

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These claims recite that the at least one immunogen together with the B subunits is present in sufficient quantity for the recited induction. Thus, "sufficient quantity" is analogous to "effective amount." See M.P.E.P. § 2173.05(c)(III).

As to the assertion that claims 12 and 23 are in improper Markush format, Applicants note that these claims do not contain Markush language. Applicants submit that these claims involve proper alternative language. "Markush language" is only one example of permissible alternative language. See M.P.E.P. § 2173.05(h). "Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims." Id. Applicants submit that the scope of the present language is clear, and thus the present language is proper alternative language.

In view of the above, Applicants respectfully request that this ground of rejection be withdrawn.

Response to § 102 Rejections

Response to Tamura

Claims 10-16 and 21-23 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,182,109 to *Tamura et al.* According to the Office, the "recitations of 'particulate' and 'recombinant DNA methods' [are viewed] as process limitations." Office Action at page 6. The Office asserts that *Tamura* teaches "a vaccine composition comprising the LTB heat-labile toxin B subunit from *E. coli* and influenza hemagglutinin (HA) antigens." Id. at 7. The Office also asserts that limitations "such as 'free from A subunit and toxic LT holotoxin', 'characteristic of *E. coli*' and 'characteristic of micro-organism' would be inherent in the vaccine composition" of *Tamura*. Id. According to the Office, the "products of the prior art reference appear to be the same as the product

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claimed by applicant because they appear to possess the same or similar functional characteristics . . . ." Id.

The Office also asserts that the "purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art." Id. According to the Office, even if Applicants' "product is of a higher purity than that of the prior art product, applicant's product would have been prima facie obvious over the product of the prior art since one of ordinary skill in the art, being motivated by the expectation of success and the attainment of greater specific activity with increased purity, could have used conventional techniques in the product art to further purify and characterize the product." Id.

Citing *In re Best*, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 205 USPQ 594 (CCPA 1980), the Office asserts that "the burden is on applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics of the claimed product." Id. at 8.

Method claims 17-20 are also rejected under 35 U.S.C. § 102(b) as anticipated by *Tamura*. According to the Office, *Tamura* teaches "a method of preparing a vaccine comprising combining one or more immunogens with heat-labile toxin subunit B from *E. coli* or cholera toxin subunit B." Id.

Applicants respectfully traverse these rejections.

Concerning claim construction, Applicants submit that "recombinant DNA methods" of dependent claim 11 should be interpreted as a product-by-process recitation and not a process limitation. Regarding "particulate," Applicants submit that

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this language is not a process limitation. In this regard, the present application at page 4, lines 19-22, states:

> As defined herein, "particulate" means any association of viral, bacterial, or fungal antigens characteristic of the micro-organisms. More in particular, the term "particulate immunogen" comprises aggregates, clusters, micelles, virosomes, rosettes, virus-like immunogen particles, and the like.

Accordingly, "particulate" and "particulate immunogen" are not process limitations.

With the above in mind, regarding independent claims 10 and 17-22, Applicants respectfully submit that *Tamura* fails to disclose at least one particulate immunogen. See *Tamura* at, e.g., cols. 2-3; and col. 10, lines 18-22. For at least this reason, *Tamura* fails to anticipate the present invention.

Regarding all the claims, the Office is reminded that in order for inherency to be present the Examiner has the burden of showing that the result indicated by the Examiner is the necessary result, and not merely a possible result. *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999). Further, the fact that a prior art article may inherently have the characteristics of the claimed product is not sufficient. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Int. 1986).

As the Board of Patent Appeals and Interferences stated in *Ex parte Levy*, 17 USPQ2d 1461, 1463-1464 (Bd. Pat. App. & Int. 1990) (citations omitted) (emphasis in original):

> However, the initial burden of establishing a prima facie basis to deny patentability to a claimed invention rests upon the examiner. In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

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Thus, as mentioned above, for inherency to be present, an Examiner has the burden to show that the allegedly inherent characteristic is a necessary result, and not merely a possible result.

In the instant case, the Office does not provide any reasoning as to why *Tamura* necessarily discloses B subunits that are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin. For this reason alone, the rejection should be withdrawn as inappropriate.

Furthermore, *Tamura* does not disclose that its B subunits are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin. In fact, *Tamura* discloses that CT is ten or more times more effective than B subunit of cholera toxin (CTB) to increase HI antibodies production. *Tamura* at col. 5, lines 22-26. Since inherency requires that something be a necessary result, and not merely a possible result, the Office has failed to show that the B subunits of *Tamura* are inherently free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin.

Still further, Tamura and his co-workers determined that LTB and CTB did not have adjuvant activity without the presence of a holotoxin. In particular, they determined that when LTB from recombinant sources (and therefore, completely free of even a trace amount of A subunit) was used, a trace of holotoxin had to be added in order for the LTB to exert mucosal activity upon intranasal co-administration with the soluble HA antigen. Present application at pages 3-4.

Tamura and his co-workers also determined that CTB alone, i.e., without CT holotoxin, had little adjuvant activity. In particular, Tamura and his co-workers stated:

> These results demonstrate that CTB itself shows little adjuvant activity, suggesting that the commercial CTB used

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> in the previous studies was contaminated with about 0.1 % of CT . . . .

TAMURA et al., "Synergistic action of cholera toxin B subunit (and *Escherichia coli* heat-labile toxin B subunit) and a trace amount of cholera whole toxin as an adjuvant for nasal influenza vaccine", *Vaccine*, 12:5, 419-426, 424 (1994), which was submitted with the September 26, 2000, Information Disclosure Statement. Thus, Tamura and his co-workers believed that a trace of holotoxin was necessarily present for CTB adjuvant activity.

Similarly, Tamura and his co-workers determined that LTB alone, i.e., without CT holotoxin, also had little adjuvant activity. It was shown that an LTB preparation with a trace amount of CT acted similarly to CTB with a trace amount of CT as an adjuvant for nasal Ab responses. Id. at 425; and Id. at Fig. 5. Tamura and his co-workers, therefore, determined that a trace of holotoxin was necessarily present for LTB adjuvant activity.

In another article, Tamura and his co-workers concluded that CTB or LTB alone, i.e., without LT holotoxin, had little adjuvant activity. TAMURA et al., "*Escherichia coli* heat-labile enterotoxin B subunits supplemented with a trace amount of the holotoxin as an adjuvant for nasal influenza vaccine," *Vaccine*, 12:12, 1083-1089, 1088 (1994), which was submitted with the September 26, 2000, Information Disclosure Statement. Thus, Tamura and his co-workers believed that a trace of holotoxin was necessarily present for LTB or CTB adjuvant activity. Accordingly, they determined that the presence or absence of holotoxin affects the properties of the compositions.

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In contrast to Tamura's work, Applicants have found that holotoxin is not necessary for LTB or CTB adjuvant activity. For instance, page 4, lines 4-13, of the present application states:

> Surprisingly, it was found that isolated LTB from recombinant origin and therefore completely free of A subunit, does possess powerful immunoadjuvant activity depending on the nature or presentation form of the intranasally co-administered immunogen.
>
> For example, adjuvant activity towards freely mixed small soluble antigens, such as ovalbumin or the soluble ectodomain of the envelope glycoprotein of human immunodeficiency virus (gp120), is low and often undetectable. On the other hand, it was found that LTB does exert very powerful adjuvant activity towards freely mixed large aggregated or particulate immunogens. These immunogens include influenza virus subunit antigen and keyhole limpet hemocyanin (KLH).

Thus, Applicants have been able to attain LTB or CTB adjuvant activity without relying on the presence or contribution of a holotoxin.

Moreover, Applicants note that Tamura and his co-workers teach away from the present invention. As noted above, they teach that a holotoxin is necessary to obtain adjuvant activity. Since the present claims require the B subunits to be free of toxic LT holotoxin and/or toxic CT holotoxin, *Tamura* cannot teach or suggest the presently claimed invention. Further, regarding independent claims 10 and 17-22, *Tamura* fails to disclose or suggest at least one particulate immunogen. Applicants therefore have shown at least one novel and nonobvious difference.

Although the claims are allowable over *Tamura* for the reasons discussed above, a few more comments regarding the burden of proof are in order. As noted above, the Office, relying on *In re Best* and *In re Fitzgerald*, asserts that the burden is on

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Applicants to show a novel or nonobvious difference. Contrary to the assertions of the Office, Applicants respectfully submit that in the present case the burden is on the Office to establish inherency, as discussed above. *In re Best* and *In re Fitzgerald* are distinguishable from the present situation.

Furthermore, the burden does not shift to Applicants based on the alleged similarity between the processes and products of the present invention and *Tamura*. In particular, the Office has failed to show that the compositions of *Tamura* are made by a substantially identical process. For instance, the Office has failed to show that *Tamura* discloses at least one particulate immunogen, and that the B subunits of *Tamura* are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin. Thus, the burden remains with the Office to show inherency. In this case, the Office cannot show inherency for the reasons discussed at length above.

In view of the above remarks, Applicants respectfully request that this anticipation rejection be withdrawn.

Furthermore, regarding the assertion that it would have been prima facie obvious to increase purity to increase activity, Applicants note that the present rejection has been made under 35 U.S.C. § 102 based on anticipation. This statement of the Examiner, however, appears to suggest that the teachings of *Tamura* require modification. Such rejections, however, are made under 35 U.S.C. § 103. If this ground of rejection is relied on in a future Office Action, Applicants expect that such an Office Action would be made non-final.

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Response to KIKUTA and HIRABAYASHI

Claims 22 and 23 are rejected under 35 U.S.C. § 102(b) as being anticipated by KIKUTA et al., *Vaccine*, 8:595-599 (1990), or HIRABAYASHI et al, *Vaccine*, 8: 243-248 (1990). According to the Office, "[c]haracteristics such as free of A subunits and LT and CT holotoxin would be inherent in the vaccine composition of the prior art references." Office Action at page 9.

Applicants traverse these grounds of rejection for reasons similar to those discussed above for *Tamura*.

For example, regarding claim 22, Applicants respectfully submit that KIKUTA and HIRABAYASHI fail to disclose at least one particulate immunogen. KIKUTA and HIRABAYASHI both use the same method as *Tamura* to prepare their immunogen. See KIKUTA at, e.g., 595; and HIRABAYASHI at, e.g., 243. That is, all three employ the method of DAVENPORT et al., *J. Lab. & Clin .Med.*, 63(1):5-13 (1964), mentioned in the present application at page 3, line 26. Applicants submit that this immunogen is not a "particulate" immunogen, as required in claim 22. For at least this reason, these documents fail to anticipate these claims.

Further, Applicants respectfully submit that KIKUTA and HIRABAYASHI fail to inherently disclose vaccine compositions that are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin, for reasons similar to those discussed above. In this regard, Tamura is listed as a co-author for both KIKUTA and HIRABAYASHI. Furthermore, KIKUTA and HIRABAYASHI are discussed in the present application at pages 3-4 as being the work of Tamura and his-coworkers that requires the presence of a trace amount of holotoxin.

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In view of the above, Applicants respectfully request that these grounds of rejection be withdrawn.

Response to NASHAR

Claims 10-18 and 21-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by NASHAR et al., *Vaccine*, 11(2):235-240 (1993). According to the Office, "[c]haracteristics such as free from A subunits and LT holotoxin . . . would be inherent in the vaccine and method of NASHAR." Office Action at page 10. Applicants traverse this ground of rejection.

Regarding independent claims 10 and 17-22, Applicants respectfully submit that NASHAR fails to disclose at least one particulate immunogen. See NASHAR at, e.g., 236 and 239. For at least this reason, NASHAR fails to anticipate the present invention.

Additionally, Applicants respectfully submit that NASHAR fails to inherently disclose vaccine compositions that are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin, for reasons similar to those discussed above. In this regard, NASHAR discloses that additional adjuvants, such as CT holotoxin, may be necessary to attain adjuvant activity. NASHAR at 238, first column.

Regarding LT holotoxin, NASHAR fails to specify that its compositions are free of LT holotoxin. Furthermore, NASHAR was published before the above-discussed findings of Tamura and his co-workers that LTB and CTB adjuvant activity requires a trace amount of holotoxin. Thus, NASHAR, like Tamura and his co-workers, may not have appreciated that a trace amount of holotoxin was present in the compositions. In this regard, NASHAR states that Tamura and his co-workers have conducted the most

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comprehensive studies on the adjuvant effect of CTB. Id. NASHAR therefore fails to disclose vaccine compositions that are inherently free of holotoxin.

In view of the above, Applicants respectfully request that this ground of rejection be withdrawn.

Response to Hirst

Claims 10-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 90/06366 to *Hirst et al*. According to the Office, *Hirst* teaches "vaccine compositions comprising fusion proteins (immunogens which can comprise antigens from influenza viruses, Herpes Simplex Viruses and hepatitis viruses) and heat-labile subunit B toxin from *E. coli* (LTB) (pages 2-8)." Office Action at page 11. Applicants traverse this ground of rejection.

Regarding independent claims 10 and 17-22, Applicants respectfully submit that *Hirst* fails to disclose at least one particulate immunogen. See *Hirst* at, e.g., page 3. For at least this reason, *Hirst* fails to anticipate the present invention.

Moreover, Applicants respectfully submit that *Hirst* fails to inherently disclose vaccine compositions that are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin, for reasons similar to those discussed above. *Hirst* fails to specify that its compositions are free of holotoxin that is necessary for adjuvant activity according to Tamura, his co-workers, and NASHAR.

In this regard, *Hirst* was filed before the above-discussed findings of Tamura and his co-workers that LTB and CTB adjuvant activity requires a trace amount of holotoxin. Thus, *Hirst*, like Tamura and his co-workers, may not have appreciated that a trace amount of holotoxin was present in the compositions.

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Even though *Hirst* involves fusion proteins such that one might argue that there is an apparent distinction between *Hirst* and some of the work of Tamura and his co-workers, this distinction does not establish that the compositions of *Hirst* were free of toxic LT holotoxin and/or toxic CT holotoxin. In this regard, the activity of the fusion proteins of NASHAR depends on the presence of additional adjuvants such as CT. NASHAR at 238. *Hirst* therefore fails to disclose vaccine compositions that are inherently free of toxic LT holotoxin and/or toxic CT holotoxin.

In view of the above, Applicants respectfully request that this ground of rejection be withdrawn.

Response to Fujisawa

Claims 10-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,241,053 to *Fujisawa et al.* According to the Office, *Fujisawa* teaches "fusion proteins [sic, protein] compositions produced and expressed recombinantly, comprising the gene encoding LTB and glycoprotein D from herpes simplex virus." Office Action at page 11. Applicants traverse this ground of rejection.

Regarding independent claims 10 and 17-22, Applicants respectfully submit that *Fujisawa* fails to disclose at least one particulate immunogen. See *Fujisawa* at, e.g., col. 2. For at least this reason, *Fujisawa* fails to anticipate the present invention.

Additionally, Applicants respectfully submit that *Fujisawa* fails to inherently disclose vaccine compositions that are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin, for reasons similar to those discussed above. *Fujisawa* fails to specify that its compositions are free of holotoxin that is necessary for adjuvant activity according to Tamura, his co-workers, and NASHAR.

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In this regard, *Fujisawa* was filed before the above-discussed findings of Tamura and his co-workers that LTB and CTB adjuvant activity requires a trace amount of holotoxin. Thus, *Fujisawa*, like Tamura and his co-workers, may not have appreciated that a trace amount of holotoxin was present in the compositions.

Even though *Fujisawa* involves fusion proteins such that one might argue that there is an apparent distinction between *Fujisawa* and some of the work of Tamura and his co-workers, this distinction does not establish that the compositions of *Fujisawa* were free of toxic LT holotoxin and/or toxic CT holotoxin. As discussed above, the activity of the fusion proteins of NASHAR depends on the presence or absence of additional adjuvants such as CT. *Fujisawa* therefore fails to disclose vaccine compositions that are inherently free of toxic LT holotoxin and/or toxic CT holotoxin.

Furthermore, the Office has failed to show that the compositions of *Fujisawa* are made by a substantially identical process. Among other differences, the Office has failed to show that *Fujisawa* discloses at least one particulate immunogen, and that the B subunits of *Fujisawa* are free of toxic LT holotoxin and/or toxic CT holotoxin.

In view of the above, Applicants respectfully request that this ground of rejection be withdrawn.

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Conclusion

Applicants respectfully request reconsideration of this application and the timely allowance of all pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: October 2, 2002

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APPENDIX

Please replace the second full paragraph of page 12 with the following new paragraph:

Virus titration in nose and lung homogenates was carried out on MDCK cells which were cultured on EPISERF cell culture medium (Life Technologies, PAISLY, Scotland) in microtitration plates by two-step dilutions, and by subsequent endpoint determination using haemagglutination with guinea pig [erythocytes] erythrocytes.

12. (Amended) The vaccine composition according to claim 10 or claim 11, wherein the at least one particulate immunogen comprises a viral antigen, a bacterial antigen, or a fungal antigen, or a combination thereof.

13. (Amended) The vaccine composition according to claim 10, wherein the at least one particulate immunogen is derived from at least one infective agent which causes a disease which is transmitted by mucosal infection.

14. (Amended) The vaccine composition according to claim 10, wherein the at least one particulate immunogen is characteristic of a micro-organism which causes a disease which is transmitted by mucosal infection.

15. (Amended) The vaccine composition according to claim 10 or claim 11, wherein the at least one particulate immunogen provides immunization against a disease which is transmitted by mucosal infection.

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16. (Amended) The vaccine composition according to claim 15, wherein the at least one particulate immunogen comprises at least one influenza [antigens] antigen.

17. (Amended) A method for the induction of a systemic immunoglobulin response against [an] at least one immunogen in a human or animal host in need of such induction, comprising [the step of]:

administering to mucosal tissue of the host said at least one immunogen in [a] particulate form and an adjuvanting amount of B subunits of heat-labile enterotoxin characteristic of *E. coli,* wherein said B subunits are free of A subunit and toxic LT holotoxin, and wherein said at least one immunogen together with said B subunits is present in sufficient quantity for said induction.

18. (Amended) A method for the induction of a common mucosal immune response against [an] at least one immunogen in a human or animal host in need of such induction, comprising [the step of]:

administering to mucosal tissue of the host said at least one immunogen in [a] particulate form and an adjuvanting amount of B subunits of heat-labile enterotoxin characteristic of *E. coli,* wherein said B subunits are free of A subunit and toxic LT holotoxin, and wherein said at least one immunogen together with said B subunits is present in sufficient quantity for said induction.

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19. (Amended) A method of preparing a vaccine for the induction of a systemic immunoglobulin response against [an] at least one immunogen in a human or animal host upon mucosal administration of said vaccine, comprising [the step of]:

combining said at least one immunogen in [a] particulate form and an adjuvanting amount of B subunits of heat-labile enterotoxin characteristic of *E. coli,* wherein said B subunits are free of A subunit and toxic LT holotoxin, and wherein said at least one immunogen together with said B subunits is present in sufficient quantity for said induction.

20. (Amended) A method of preparing a vaccine for the induction of a common mucosal immune response against [an] at least one immunogen in a human or animal host upon local mucosal administration of said vaccine, comprising [the step of]:

combining said at least one immunogen in [a] particulate form and an adjuvanting amount of B subunits of heat-labile enterotoxin characteristic of *E. coli,* wherein said B subunits are free of A subunit and toxic LT holotoxin, and wherein said at least one immunogen together with said B subunits is present in sufficient quantity for said induction.

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